REMARKS

Claim Rejections

35 U.S.C. § 102

Applicants respectfully submit that amended claims 80, 89, 103, 109 and new claims 111-118 are not anticipated by either JP-8-268,886 or U.S. Patent No. 6,521,271. Applicants respectfully request that rejection of the claims under 35 U.S.C. § 102 be withdrawn.

JP 08-268,886

In particular, the Office action maintains rejection of claims 80 and 82 as allegedly anticipated by JP 08-268,886 ('886).

Applicants respectfully disagree. Claim 82 is cancelled in the Amendment and Request for Continued Examination submitted November 7, 2005, without prejudice or disclaimer to pursuing the invention of claim 82 in continuing or divisional patent applications. Therefore, Applicants have overcome this ground of rejection for claim 82 and respectfully request it be withdrawn.

The Office action alleges that claim 80 is anticipated because JP-886 teaches that satigrel or aspirin may be used to treat a "keloid." (Page 5 of the Office action mailed 6/7/05). However, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131.01. JP-886 does not disclose, either expressly or inherently, each and every element of amended Claim 80. In particular, amended claim 80 is not directed to a keloid but rather is directed to a closed wound that is caused by laceration; by avulsion; by burn; by radiation; by chemical facial peel; or by accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar or a fibrotic scar. As further support demonstrating that

JP-886 does not disclose, either expressly or inherently, any "closed wound," Applicants respectfully direct the Examiner's attention to the Declaration of Raphael C. Lee, M.D., Sc.D., submitted herewith. From paragraphs 13-16, Dr. Lee explains:

13. JP-886 does not provide any example of treatment of a keloid scar, or for that matter, any type of "closed wound" as that term is used in the claims of the above-identified application. Rather, the only example in JP-886 describes intravenous administration of satigrel to a punch wound on the auricle of a rabbit. More specifically, this example describes that 21 mature domestic rabbits underwent a drum fixation procedure. In particular, in each rabbit, an auricle was shaved and the rabbit was then attached to a metallic drum. The auricle was punched circularly by a puncher. After a punch was made a small-sized scalpel was used to peel the skin off of the outer side surrounding the perimeter of the punch hole. Then, for three weeks, on a once daily basis, satigrel sodium was administered.

14. One of ordinary skill in the art would understand that administration of satigrel on a daily basis, as carried out in the only example in JP-886 (described above), would prevent the punch and skinless area surrounding the punch from reepithelializing during the three week observation period. Therefore, the only example illustrating any suppression of neovascularization is based on treatment of an *open* wound, *i.e.* a wound that has not reepithelialized.

15. As explained at page 6 of the specification and paragraph 7 of this declaration, within the meaning of the claims in the above-identified application, "[a] wound is 'closed' after an open wound has been re-epithelialized."

16. In my opinion, one of ordinary skill in the art would not rely on the solitary example to extrapolate from JP-886 that aspirin might be used to reduce the size and improve the appearance of a *different type of wound*, *e.g.*, a "closed wound."

Thus, JP-886 does not disclose reducing the size or improving the appearance of any "closed wound," either expressly or inherently.

Further, claim 80 is amended to recite that the composition consisting essentially of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent is topically administered in an amount ranging from about 0.1 percent to about 10 percent by weight of a pharmaceutically acceptable carrier. JP-886 does not disclose

topical administration of any of the non-steroidal anti-inflammatory agents listed in claim 80 at such a dosage range.

JP-886 does not disclose each and every element of the invention of claim 80, and therefore, does not anticipate the invention of claim 80.

U.S. Patent No. 6,521,271

Claims 80, 82, 87, and 93 stand rejected under 35 U.S.C. § 102(e) as anticipated by US Patent No. 6,521,271 (the "'271 patent"). Applicants previously argued that the '271 patent does not anticipate the claims because this patent does not teach that salicylic acid may be used to reduce the size or improve the appearance of a "closed wound." In addition, Applicants previously argued that the '271 patent teaches that *turmeric compounds* can be used to treat scars and that salicylic acid may be used to enhance the penetration of the turmeric compound into the scar, not to reduce the size or improve the appearance of the scar. The Office action rejects Applicants argument, noting that claim 80 uses the open language "comprising," which "permits the presence of other ingredient *(sic)*, active or inactive even in major amounts." (Office action mailed 6/7/05, page 6).

Applicants respectfully disagree that the '271 patent anticipates the invention at least for the reasons made of record in the Amendment and Response submitted February 14, 2005. In any event, to expedite prosecution, and without prejudice or disclaimer to pursuing the invention of claims 80, 82, 87, and 93 in continuing or divisional applications, Applicants have cancelled claims 82, 87, and 93 and have amended claim 80 in the Amendment and Request for Continued Examination submitted November 7, 2005. As amended, claim 80 is directed to a method involving topical administration of a composition *consisting essentially of* (i) a pharmaceutically acceptable carrier, and (ii) at least one of a specific group of non-steroidal anti-inflammatory agents, wherein the at least one non-steroidal anti-inflammatory agent is administered in an amount ranging from about 0.1% to about 10% by weight of the pharmaceutically acceptable carrier. Applicants respectfully submit that because the '271 patent does not teach that any of

the non-steroidal anti-inflammatory agents listed in claim 80 can be used by themselves to reduce the size or improve the appearance of a closed wound, amendment of claim 80 to recite the closed language "consisting essentially of" overcomes the Examiner's rejection of claim 80.

Therefore, Applicants respectfully submit that pending claim 80 and new claims 111-118, which incorporate all elements of claim 80, are not anticipated by the '271 patent. Applicants respectfully request that rejection of claim 80 under 35 U.S.C. § 102 be withdrawn.

35 U.S.C. § 103

Applicants respectfully submit that amended claims 80, 89, 103, 109 and new claims 111-118 are not rendered obvious by any of DE 27 07 537, JP-8-269,886 or U.S. Patent No. 6,521,271, either alone or in combination with U.S. Patent No. 5,552,162. Applicants respectfully request that this ground of rejection be withdrawn.

DE 27 07 537

In particular, claims 103, 107, and 108 stand rejected under 35 U.S.C. § 103 as being obvious in view of DE 27 07 537 ("DE 537"). Applicants respectfully disagree that the DE 537 reference renders the presently claimed invention obvious under 35 U.S.C. § 103. Claim 103 is amended in the Amendment and Request for Continued Examination submitted November 7, 2005, to include the limitations of claims 107 and 108. Claims 107 and 108 are cancelled therein without prejudice or disclaimer to pursuing the inventions of those claims in continuing or divisional applications.

To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach all the claim limitations. MPEP § 2142.

DE 537 does not render pending claim 103 or new claims 111-118 obvious because there is no motivation or suggestion to apply the teachings of the DE 537 outside of *acne* scarring; there is no reasonable expectation of success that applying the teachings of DE 537 outside of acne scarring would reduce the size or improve the appearance of a closed wound as that term is used in the claims; and DE 537 does not teach all the claim limitations of claim 103 or new claims 111-118.

DE 537 is directed to treatment of acne, tinea versicolor, seborrheic dermatitis, and other disorders associated with hyperplasia that has been brought about by infected sebaceous glands. (Page 7, DE 537). There is no suggestion or motivation to apply the teaching of DE 537 to reduce the size or improve the appearance of a closed wound that is caused by laceration, avulsion, burn, radiation, chemical facial peel, or accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar, or a fibrotic scar. As explained more fully below, acne treatments, such as that described in DE 537, are directed at aiding in or promoting the removal or shedding of dead skin cells, whereas reduction in the size or improvement in the appearance of a closed wound as that term is used in the claims of the present invention is based on promoting cell growth.

An understanding of the etiology of acne and the mode of action of salicylic acid in acne treatments further demonstrates that there is no motivation to apply the teaching that salicylic acid can be used in an acne treatment to the types of closed wounds to which the claims are directed and also demonstrates there is no reasonable expectation of success in applying the teachings of DE 537 outside acne scarring. As stated above, submitted herewith is a declaration of Raphael C. Lee, M.D., Sc.D. In his declaration, Dr. Lee explains both the etiology of acne and the mode of action of salicylic acid in acne treatments. Specifically, from paragraphs 34-36 of his declaration, Dr. Lee explains:

> 34. . . . It is commonly known and widely accepted that acne forms inside a skin pore as a result of abnormal desquamation of cells of the follicular epithelium. More specifically, a skin pore is an opening in the skin

through which a very fine hair typically will grow and sweat glands will drain. Skin pores are connected to sebaceous glands, which produce an oily sebum that lubricates the hair and skin. Acne occurs when the sebaceous glands produce thick highly viscous oil that when combined with the desquamated cells, forms a plug that obstructs further drainage of sebum. This results in an enlarged, blocked pore called a comedo. Plugged pores create a breeding ground for skin bacteria. As the bacteria flourish in the comedo, skin infection begins leading to pain, inflammation, and scarring.

35. Existing acne treatments focus on *slowing* down the skin's production of oil, and *encouraging* rapid desquamation (*e.g.* shedding of dead skin cells), or *fighting* bacteria. Increasing desquamation leads to larger diameter skin pores and thinner epidermis and better drainage of the pore.

36. More specifically, salicylic acid is lipid soluble, which means it can penetrate into a pore containing sebum and loosen desquamated skin cells built up inside the pore. Indeed, it is well *understood and widely accepted in the art that salicylic acid treats acne by loosening the intercellular cement material present in the pores, increasing the diameter of the skin pore, and by thinning the epidermis*, which drains the plugged pores and prevents further plugs from forming. *By draining the skin pores and removing the infection, inflammation and fibrous tissue formations are reduced. Thus, any treatment that would cure acne would also indirectly prevent acne scaring. See e.g.,* Davies, M. and Marks, R. "Studies on the effect of salicylic acid on normal skin." *Br. J. Dermatol.* 1976. 95(2):187-92 and Roberts *et al.,* "Detection of the action of salicylic acid on the normal stratum corneum." *Br. J. Dermatol.* 1980. 103(2):191-6.

Indeed, Dr. Lee declares that as one of at least ordinary skill in the art, it is his opinion that, "based on the understood mode of action of salicylic acid in acne treatments (discussed above), it would not be expected that salicylic acid could be used to treat either an external wound, including one that has reepithelialized, or a scar caused by an external trauma." (Paragraph 37, Lee Declaration submitted herewith). Therefore, there is no motivation, either in the art or in the DE 537 reference, to apply the teachings of DE 537, that salicylic acid can be used to treat acne, to reduce the size or improve the appearance of a "closed wound."

Dr. Lee's declaration also demonstrates that even if one of ordinary skill in the art were motivated to apply the teachings of DE 537 to treat a "closed wound," such a person

would not have a *reasonable* expectation of success. According to Dr. Lee, it is well-known that salicylic acid should not be used on wounds with a weakened external barrier, such as wounds that have recently re-epithelialized, because use of salicylic acid on inflamed, irritated, or infected areas of the skin can cause severe irritation. *See* paragraphs 38-42 of the Lee Declaration, which reference Rhein *et al.,* "Targeted delivery of salicylic acid from acne treatment products into and through skin: role of solution and ingredient properties in relationships to irritation." *J. Cosmet Sci.* 2004. 55(1):65-80 and USP DI Advice for the Patient [Internet]. [Greenwood Village (CO)]: Thomson MICROMEDEX; ©2005. Salicylic acid; [revised 2005 Jan 19; cited 2005 October 7]; [~ 8 p.]. Available from: http://www.nlm.nih.gov/medlineplus/druginfo/uspdi/202516.html (attached).

Therefore, as Dr. Lee explains at paragraph 38, one of ordinary skill in the art would expect that salicylic acid would cause severe irritation of the skin if the salicylic acid was administered when the epidermal barrier was weakened or lost, as happens with external wounds such as the closed wounds to which claim 103 and new claims 111-118 are directed. Indeed, "one of ordinary skill in the art in 2001 would expect salicylic acid to delay the wound healing process, irritate and exacerbate, not alleviate, scarring in skin tissues that are in recovery from an external trauma." (Paragraph 39, Lee Declaration submitted herewith). *See also* paragraph 29 of the Lee Declaration (discussing the Lee, KH "Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." J Pharm Sci. 1968 Jun;57(6):1042-3 reference, which teaches that topical application of a composition comprising 3% salicylic acid *retards* the wound healing process).

From paragraphs 40-45, Dr. Lee reviews the wound healing process and explains, at paragraphs 46-47, that his opinion is based on the understanding one of ordinary skill in the art would have of this process:

> 46. Additionally, in my opinion, one of ordinary skill in the art would understand that during the initial phases of wound healing, the newly forming epidermis covering and surrounding the wounded area is extremely thin and sensitive and susceptible to acidic agents such as salicylic acid, which causes desquamation of the epidermis, and

irritates the wound. These effects lead to delayed wound healing and prolonged inflammation. *See e.g.,* Lee, KH. "Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." *J Pharm Sci.* 1968 Jun;57(6):1042-3.

47. Therefore, it is my opinion that in 2001, a skilled artisan would not treat a "closed wound," particularly during the inflammatory and early transitional repair phases, with a treatment such as salicylic acid, which is known to delay the wound healing and cause severe irritation when applied to inflamed sensitive skin.

Paragraphs 46-47, Lee Declaration submitted herewith.

Thus, one of ordinary skill in the art would neither be motivated to use salicylic acid to treat a closed wound, nor would such a person have a *reasonable* expectation of success in using salicylic acid to reduce the size or improve the appearance of a "closed wound."

Third, DE 537 does not disclose all elements of claim 103 because DE 537 does not disclose either a kit or reducing the size or improving the appearance of any closed wound caused by laceration; by avulsion; by burn; by radiation; by chemical facial peel; or by accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar or a fibrotic scar.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the DE 537 reference. Hence, Applicants respectfully submit that neither pending claim 103 nor new claims 111-118, which incorporate the elements of claim 103, are obvious in view of DE 537. Applicants respectfully request that this ground of rejection be withdrawn.

JP 08-286,886

Claims 87, 89, 92, 101-103, and 107-110 stand rejected under 35 U.S.C. § 103 as being obvious over JP '886 in view of U.S. Patent No. 5,552,162 (the "'162 patent"). Applicants respectfully disagree that the combination of JP '886 and the '162 patent renders the present invention obvious.

Claims 87, 92, 101, 102, 107-108 and 110 are cancelled without prejudice or disclaimer in the Amendment and Request for Continued Examination submitted November 7, 2005. Claims 89, 103 and 109 are not obvious under 35 U.S.C. §103 because there is no suggestion or motivation to modify the teaching of JP '886 to arrive at the claimed invention. In particular, as discussed above at pages 2-7, JP-886 does not teach any of the closed wounds to which pending claims 89, 103, or 109 are directed. Although the Office relies on JP-886 for the teaching that satigrel or aspirin may be used to treat a "keloid," (Page 5 of the Office action mailed 6/7/05), as amended, the claims are not directed to treating a keloid. Further, one of ordinary skill in the art would not be motivated to apply the teachings of JP-886 to the closed wounds of the claims. Specifically, JP-886 only discloses administration of satigrel to an *open* punch wound on a rabbit auricle. One of ordinary skill in the art would not be motivated to apply the teachings of this solitary example to reduce the size and improve the appearance of any of the *closed* wounds to which claims 89, 103, or 109 are directed. Indeed, Dr. Lee expresses this view at paragraphs 13-16 of his declaration. *See also* page 3 above.

Further, even if one of ordinary skill in the art were motivated to modify the teachings of JP-886 and apply it to reduce the size and improve the appearance of a "closed wound," one of ordinary skill in the art would not have a *reasonable* expectation of success. First, as Dr. Lee declares: "JP-886 does not provide any example of treatment of a keloid scar, or for that matter, any type of "closed wound." (Paragraph 13, Lee Declaration). Further, as discussed above, the only example in JP-886 describes intravenous administration of satigrel to an *open* punch wound on the auricle of a rabbit. Specifically, this example describes that 21 mature domestic rabbits underwent a drum fixation procedure. In particular, in each rabbit, an auricle was shaved and the rabbit was then attached to a metallic drum. The auricle was punched circularly by a special puncher. After a punch was made a small-sized scalpel was used to peel the skin off of the outer side surrounding the perimeter of the punch hole. Then, for three weeks, on a once daily basis, satigrel sodium was administered.

JP-886 reports that angiogenesis was suppressed when satigrel sodium was administered and therefore, asserts that "it was shown that it can become prevention

treatment improving agents for stomach cancer, a lung cancer, a hepatic carcinoma, a colon cancer, a rectal cancer, a pancreatic cancer, a prostatic cancer, a bladder cancer, a renal cancer, an ovarian tumor, a uterine cancer, a breast cancer, skin cancer, malignant melanoma or a basal cell carcinoma, keloid, inflammation, diabetic retinopathy, etc."

As Dr. Lee explains at paragraphs 27-29 of his declaration, one of ordinary skill in the art will appreciate that each disease included within the above-identified wide variety of diseases will have its own etiology and therefore its own unique treatment and prevention regimen. Therefore, one of ordinary skill in the art would not rely on the JP-886 reference for teaching treatment or prevention of all of the listed diseases:

27. Further, in my opinion, one of ordinary skill in the art would doubt the claim in JP-886 that the large number and variety of diseases described therein could be treated or prevented by administering satigrel or aspirin. In particular, in the one example described in JP-886, discussed above at paragraph 13, it is reported that angiogenesis was suppressed when satigrel sodium was administered. Based on this example, JP-886 claims that "it was shown that it can become prevention treatment improving agents for stomach cancer, a lung cancer, a hepatic carcinoma, a colon cancer, a rectal cancer, a pancreatic cancer, a prostatic cancer, a bladder cancer, a renal cancer, an ovarian tumor, a uterine cancer, a breast cancer, skin cancer, malignant melanoma or a basal cell carcinoma, keloid, inflammation, diabetic retinopathy, *etc.*" (Paragraph 39, JP-886).

28. It is my opinion that one of ordinary skill in the art would not rely on the teachings of JP-886 because such a person would doubt that satigrel or its salts, aspirin or its salts, or some combination thereof can be used to treat or prevent the enormous variety of diseases claimed to be treated or prevented in JP-886.

29. In particular, in my view, one of ordinary skill in the art would be very skeptical of JP-886 because the reference fails to provide any example that demonstrates treatment or prevention of any of the above-identified diseases.

Second, JP-886 does not teach any dosage of aspirin that might be *topically* administered to achieve the "prevention or treatment" described in JP-886. Indeed, as Dr. Lee explains, one of ordinary skill in the art would appreciate that each of the diseases claimed to be treated or prevented by JP-886 would require oral administration of aspirin or administration by injection. Dr. Lee further declares that the dosage range of aspirin disclosed in JP-886 is too low to achieve any treatment or prevention effect:

17. Additionally, one of ordinary skill in the art will appreciate that each disease included within the above-identified wide variety of diseases would be located in different parts of the body and could only be treated with aspirin or salicylic acid by *oral* administration or administration by *injection* into the blood circulation.

18. Indeed, JP-886 suggests that aspirin can be orally administered daily in an amount ranging from 0.01-2000 mg (paragraph 28 of JP-886) to suppress neovascularization and thereby treat or prevent a keloid disease. This use of aspirin is contrary to my experience as a physician during the time period preceding and including 2001.

19. Specifically, as of 2001, one of ordinary skill in the art would know that oral administration of aspirin at doses ranging from 0.01-2000 mg would neither systemically nor locally suppress neovascularization in an amount sufficient to prevent or treat any of the above-identified diseases. One of ordinary skill in the art also would appreciate that neovascularization is a normal step in the wound healing process and that the aspirin dosage range taught by JP-886 is within the normal, accepted dosage range for oral administration of aspirin. Therefore, if the teaching of JP-886 were true (i.e. that oral administration of aspirin at a dosage ranging from 0.01-2000 mg suppresses neovascularization sufficient to treat a keloid), then a person taking aspirin in that normally accepted dosage range for any reason, such as having a headache, would be expected to heal a keloid because allegedly neovascularazation would be suppressed in an amount sufficient to treat a keloid. At the same time, it would be expected that such a person would not be able to heal a wound because wound healing requires neovascularization.

20. However, in my experience as a physician, patients taking aspirin do heal wounds. Further, it is my opinion that one of ordinary skill in the art in 2001 would not have used oral administration of aspirin, in the normally accepted dosage range, as a treatment for a keloid. For example, as described in Example 4 of the above-identified application, described at pages 30-31, a patient suffering from a post-operative scar was taking 325 mg of aspirin per day to prevent thrombo-embolic post-operative complications. Although this patient was being orally administered aspirin on a daily basis, the patient's closed wound was neither "treated" nor "prevented" as claimed by JP-886.

21. Thus, the teaching of JP-886 discussed above in paragraph 19 is contrary to the knowledge and understanding that one of ordinary skill in the art would have in 2001.

22. Therefore, in my opinion, as one of at least ordinary skill in the art, JP-886 does not provide any evidence demonstrating that aspirin or any of its salts may be topically administered in an amount ranging from about 0.1 percent to about 10 percent by weight of a pharmaceutically acceptable vehicle to reduce the size or improve the appearance of a wound caused by an external trauma that has reepithelialized, *e.g.* a "closed wound."

Paragraphs 17-22 of the Lee Declaration submitted herewith. Therefore, JP-886 does not provide any *reasonable* expectation of success in treating a "closed wound." Indeed, as discussed above in paragraph 20 of the Lee Declaration, Example 4 of the present specification describes oral administration of 325 mg of aspirin per day to a patient suffering from a post-operative scar. Aspirin was administered to this patient to prevent thrombo-embolic post-operative complications, not to heal any wounds or treat or prevent any scar. Significantly, although this patient was being orally administered aspirin on a daily basis, the patient's closed wound was neither "treated" nor "prevented" as claimed by JP-886. Indeed, treatment of the patient's scar (in the form of reduction in the size of the scar and an improvement in its appearance) only was achieved when *2% salicylic acid was topically administered* in combination with a use of a hydrogel. This is a surprising result because, as Dr. Lee attests at paragraphs 23-25, one of ordinary skill in the art in 2001 would understand that at *high* concentrations, such as 3% salicylic acid as discussed below in paragraphs 24-26, aspirin (or salicylic acid) *retards* the wound healing process:

24. Further, one of ordinary skill in the art also would appreciate that at *high* concentrations, aspirin retards the wound healing process.

25. For example, in the *Journal of Pharmaceutical Science,* K.H. Lee *et al.* describe an injury similar to that discussed in the example set forth in JP-886. Specifically, Lee describes an injury where a circular piece of skin, about 5 cm in diameter, was removed from the back of Sprague-Dawley rats. The wounds remained undressed. Wound healing was measured by quantification of tensile strength (*i.e.* measurement of the force required to open a healing skin wound). Table I reports that rats receiving an oral dose of 150 mg/Kg of aspirin daily have an average tensile strength of skin wound that is about 60% that of control. Table I further reports that when the dose of aspirin was reduced to 75 mg/Kg, the average tensile strength of skin wound was about 78% that of control. Therefore, Lee concludes that aspirin retards wound healing. *See* Lee, KH. "Studies on the mechanism of action of salicylates. 3. Effect of vitamin A on the wound healing retardation action of aspirin." *J Pharm Sci.* 1968. 57(7):1238-40.

26. In a related article, KH Lee *et al.* report that approximately 6 cm incisions were made on the backs of Sprague-Dawley male rats. The incisions were allowed to cease bleeding in a normal manner and were sutured using black silk surgical thread. The wounds were left undressed. Fifty mg of sodium salicylate dissolved in a small amount of water was fed to the rats daily for 4 days through a short stomach tube. Again, wound healing was measured by quantification of tensile

strength (*i.e.* measurement of the force required to open a healing skin wound) seven days after wounding. In Table II, Lee reports that Group II, which consisted of 8 rats who were orally administered sodium salicylate, exhibited a mean tensile strength that was only 79% that of the control group of rats. Similarly, Table II reports that in Group IV, which consisted of 11 rats who were topically administered 3% salicylic acid in a non-ionic base, the mean tensile strength was only 88% that of the control group. K.H. Lee *et al.* conclude that this study shows retardation of wound healing by aspirin. *See* Lee, KH *et al.*, "Studies on the mechanism of action of salicylate. II. Retardation of wound healing by aspirin." *J Pharm Sci.* 1968. 57(6):1042-3.

Therefore, neither JP-886 nor the knowledge of one of ordinary skill in the art provides any *reasonable* expectation of success in reducing the size or improving the appearance of a "closed wound" by topically administering any of the non-steroidal anti-inflammatory agents listed in claims 80 and 103 in an amount ranging from about 0.1 percent to about 10 percent by weight of a pharmaceutically acceptable carrier.

Third, JP-886 does not disclose all elements of claims 89, 103, and 109 because JP-886 does not disclose either a kit or reducing the size or improving the appearance of any *closed* wound caused by laceration; by avulsion; by burn; by radiation; by chemical facial peel; or by accident, wherein the closed wound consists of a normal scar, a hypertrophic scar, a Dupuytren's contracture, a Peyronnie's Disease, a reactive scar, an excessive post-operative scar or a fibrotic scar. JP-886 also does not disclose topically administering a composition consisting of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent. Further, as discussed above, JP-886 neither teaches topical administration of a composition consisting essentially of a non-steroidal anti-inflammatory agent listed in claim 80 and a pharmaceutically acceptable carrier, wherein the non-steroidal anti-inflammatory agent is administered in an amount ranging from about 0.1 percent to about 10 percent by weight of the pharmaceutically acceptable carrier, nor provides any guidance for determining what range of non-steroidal anti-inflammatory agents may be topically administered to reduce the size or improve the appearance of a closed wound

The '162 patent is relied on for its teaching of "a method for improving the size and appearance of the scar . . . by covering the scar with thermal insulating material and active agent." (Page 8 of the Office action mailed 6/7/05). Therefore, the '162 patent

does not itself provide motivation for modifying the teaching of JP-886 to apply it to a "closed wound" as that term is used in the claims of the present invention. The '162 patent also does not provide any *reasonable* expectation of success in applying the teachings of JP-886 to treating the closed wound of the present claims. Even further, the '162 patent does not provide any motivation or reasonable expectation of success in reducing the size or improving the appearance of a closed wound by topically administering a composition consisting essentially of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent in an amount ranging from about 0.1 percent to about 10 percent by weight of the pharmaceutically acceptable carrier.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the JP-886 reference, either alone or in combination with the '162 patent. Hence, Applicants respectfully submit that neither pending claims 89, 103 or 109, nor new claims 111-118, which incorporate all elements of claims 89, 103 and 109, are obvious in view of JP-886. Applicants respectfully request that this ground of rejection be withdrawn.

U.S. Patent No. 6,521,271

Claims 89, 92, 93, 101-103 and 107-110 stand rejected under 35 U.S.C. § 103 as being obvious over the '271 patent in view of the '162 patent. Applicants respectfully disagree that the combination of these references renders the claimed invention obvious.

Claims 92, 93, 101-102, 107-108, and 110 are cancelled in the Amendment and Request for Continued Examination submitted November 7, 2005 and claim 80 is amended therein. Claim 89 depends from claim 80. As discussed above, claim 80 is amended to recite the closed language "consisting essentially of." Specifically, as amended claim 80 is directed to a composition consisting essentially of (i) a pharmaceutically acceptable carrier and (ii) at least one non-steroidal anti-inflammatory agent selected from the group listed in claim 80, wherein topical administration of the composition reduces the size or improves the appearance of a "closed wound."

Also as explained above at pages 7-8, and in the Amendment and Request for Reconsideration mailed February 14, 2005, the '271 patent teaches that *turmeric compounds* can be used to treat scars and that salicylic acid may be used to enhance the penetration of the turmeric compound into the scar, not to reduce the size or improve the appearance of the scar. There is no motivation to modify this teaching of the '271 patent. Further, alone or in combination, the '271 patent and the '162 patent do not provide any basis for finding a *reasonable* expectation of success in reducing the size or improving the appearance of a closed wound by topical administration of any of the non-steroidal anti-inflammatory agents listed in the claim 80. Moreover, the '271 patent, even in combination with the '162 patent, does not teach all elements of the claims. Therefore, alone or in combination with the '162 patent, the '271 patent does not render the claimed invention obvious. *See* MPEP § 2142.

More specifically, the '271 patent teaches that turmeric compounds may be used to reduce the size or improve the appearance of a scar. In fact, in every example of the '271 patent, a turmeric compound is used as the active ingredient. Moreover, although the '271 patent teaches use of salicylic acid in a composition for treating a wound, the '271 patent teaches that salicylic acid is included in the composition because it is effective as a penetration enhancer or as an exfoliant. (col. 6, ll.22-26). Specifically, at col. 4, ll. 33-50, the '271 patent teaches that the *effectiveness* of *turmeric components* can be increased by administering turmeric components in combination with various alpha and beta-hydroxy acids, because the acids act as penetration enhancers:

> [I]t is believed that, when the turmeric component(s) are combined with alpha hydroxy acids, the effective concentration of the turmerin and curcumin provides a more active composition for treatment of scars, pigmentation and aging skin. It is believed that, when combined with alpha hydroxy acid, the component(s) of turmeric (in particular curcumin and turmerin) are able to penetrate the skin and have a pronounced effect on the skin being treated that would not be achieved in the absence of the alpha hydroxy acid.

(col. 4, ll. 37-45). Significantly, the '271 patent particularly teaches that salicylic acid is a primary example of a hydroxy acid that functions as a penetration enhancer when used with a turmeric component (col. 4, ll. 48-49).

Further, at col. 9, ll. 4-9, the '271 patent teaches that salicylic acid "has been shown to aid in dead skin removal . . . and to have a keratinolytic effect that is useful for skin treatment." None of these characteristics of salicylic acid would motivate one of ordinary skill in the art to modify the teaching of the '271 patent (*i.e.* that turmeric compounds may be used to treat a scar) by using salicylic acid by itself or as the active ingredient, to reduce the size or improve the appearance of a "closed wound."

Even further, the Lee Declaration discussed above and submitted herewith provides additional evidence that one of ordinary skill in the art would not be motivated to use salicylic acid, by itself, to reduce the size or improve the appearance of a closed wound as that term is used in the present claims. *See e.g.* paragraphs 31-48 of the Lee Declaration.

In addition, none of the above-identified passages in the '271 patent provide one of ordinary skill in the art with a *reasonable* expectation of success using a non-steroidal anti-inflammatory agent selected from the group listed in claim 80 to reduce the size or improve the appearance of a closed wound.

The '162 patent is relied on for the teaching of a thermal insulating hydrogel (page 10 of the Office action mailed 6/7/05). Therefore, the '162 patent does not itself provide motivation for modifying the teaching of the '271 patent to use salicylic acid *by itself* to reduce the size or improve the appearance of a "closed wound." The '162 patent also does not provide any *reasonable* expectation of success in reducing the size or improving the appearance of a closed wound by topically administering a composition consisting essentially of a pharmaceutically acceptable carrier and at least one non-steroidal anti-inflammatory agent selected from the group listed in claim 80.

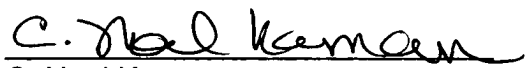
Moreover, to render a claimed invention obvious, the cited reference or combination of references must teach each and every element of the claimed invention. *See* MPEP § 2142. Neither the '271 patent, nor the '162 patent teaches or even suggests that any of the non-steroidal anti-inflammatory agents listed in claim 80 could be used *by itself* to reduce the size or improve the appearance of a "closed wound" as is required by the claims of the present invention.

Therefore, none of the three elements for establishing even a *prima* facie case of obviousness are met by the '271 patent, either alone or in combination with the '162 patent. Applicants respectfully submit that pending claims 80, 89, 103 and 109 and new claims 111-118, which incorporate all elements of pending claims 80, 89, 103, and 109, are not rendered obvious by the combination of the '271 and '162 patents and respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants believe that currently pending Claims 80, 89, 103, and 109 and new claims 111-118 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,



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